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Preliminary Results of the Hydroxyapatite Nonpolymer-Based Sirolimus-Eluting Stent for the Treatment of Single De Novo Coronary Lesions

A First-in-Human Analysis of a Third-Generation Drug-Eluting Stent System

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Objectives We sought to investigate the performance and efficacy of the third-generation polymer-free Vestasync-eluting stent (VES).

Background Recent concerns regarding the long-term safety of drug-eluting stents have been raised. Synthetic polymers have been associated with intensive inflammatory response and late stent thrombosis. Newly developed, the VES combines a stainless steel platform with a nanothin-microporous hydroxyapatite surface coating impregnated with a polymer-free sirolimus formulation (55 μm).

Methods In May 2007, 15 patients with single de novo lesion located in native coronary arteries 3.0 to 3.5 mm in diameter and ≤14 mm in length were consecutively enrolled. Primary end points included in-stent late lumen loss and in-stent percent of obstruction at 4 months. Serial angiography and intravascular ultrasound were obtained at the index procedure and repeated at 4-month follow-up.

Results Mean population age was 63.8 years; 33% of patients were diabetic. The left anterior descending artery was the prevalent target vessel (47%). Reference vessel diameter and lesion length were 2.67 ± 0.32 mm and 9.98 ± 1.98 mm, respectively. The VES was successfully implanted in all cases, and there were no procedure and in-hospital complications. Life-long aspirin and 6-month clopidogrel therapy were prescribed for all patients. At 4 months, in-stent late lumen loss was 0.30 ± 0.25 mm and percent of stent obstruction was 2.8 ± 2.2%. After up to 6 months of clinical follow-up, no major adverse cardiac event was registered.

Conclusions The third-generation VES demonstrated excellent acute results in the treatment of de novo coronary lesions. Longer follow-up with a more complex subset of patients and lesions is required to confirm these preliminary results. (J Am Coll Cardiol Intv 2008;1:545–51) © 2008 by the American College of Cardiology Foundation

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The efficacy of first-generation drug-eluting stents (DES) in reducing in-stent neointimal proliferation and therefore the need for repeat lesion revascularization is irrefutable (1,2). However, recent concerns regarding the long-term safety of the Cypher (Cordis, Johnson & Johnson, Miami Lakes, Florida) and Taxus (Boston Scientific Corporation, Natick, Massachusetts) stents have been raised (3–5).

The synthetic polymer, an essential component of these first-generation devices, has been associated with an intensive inflammatory response (6). Animal histopathology and ex-vivo model analysis have shown exacerbated positive vessel remodeling, possibly caused by local response to the polymer presence (7). Importantly, the association between exacerbated vessel enlargement and very late DES thrombosis has been recently demonstrated (8,9).

As a consequence, there is a major interest in developing new DES with greater flexibility, radiopacity, and better safety profile. Recently developed, the Vestasync-eluting stent (VES) (MIV Therapeutics, Inc., Atlanta, Georgia) combines a stainless steel platform with a nanothin-microporous hydroxyapatite surface coating impregnated with a polymer-free sirolimus formulation (55 μg).

After positive preclinical studies, this first-in-human investigation was conceived to evaluate to investigate the safety, performance, and efficacy of this third-generation polymer-free DES.

Abbreviations and Acronyms

CK = creatine kinase
CK-MB = creatine kinase-myocardial band
DES = drug-eluting stent
IVUS = intravascular ultrasound
QCA = quantitative coronary angiography
VES = Vestasync-eluting stent

Methods

Study population. In May 2007, a consecutive cohort of patients with single, de novo lesions <14 mm in length, located at native coronaries of diameters from 3.0 to 3.5 mm (by visual assessment) were consecutively enrolled in this first-in-human study. Patients should present symptoms of angina (stable/unstable) or silent ischemia clearly documented through noninvasive assessment. Patients treated within 72 h of an acute myocardial infarction and/or requiring more than 1 stent to treat the target lesion were excluded from this study. We also excluded patients who had heavily calcified lesions, lesions at bifurcations or involving the ostium of the coronary vessel, severe left ventricular dysfunction (left ventricular fraction <30%), visible thrombus, and contraindications to any of the protocol medications.

The protocol was approved by the local Ethics Committee, and written informed consent was obtained from all patients before inclusion in the study.

Device description. As with most DES systems, the Vestasync hydroxyapatite nonpolymer-based sirolimus-eluting stent system comprises 3 basic components: a platform, an antiproliferative agent, and a drug carrier. In the following text, we briefly describe all 3 components used in this novel device.

Stent platform. The GenX stainless steel (316 L) coronary artery stent (MIV Therapeutics, Inc.) is the new-generation variable geometry stent designed to minimize stent-induced arterial injury (strut thickness = 105 μm). The GenX stent is pre-mounted on a polyamide balloon catheter between 2 platinum iridium radio-opaque markers bands, nominally 0.5 mm longer than the stent. Mounted stent length and location are defined by radio-opaque marker.

Nonpolymeric drug carrier. The coating is composed of a microporous hydroxyapatite [Ca10(PO4)6(OH)2] underlying coating. Sirolimus in a biocompatible oil-based formulation is loaded into the microporous hydroxyapatite coating.

Hydroxyapatite constitutes 70% of natural bone composition and therefore posseses excellent biocompatibility. It does not invoke an inflammatory reaction or foreign body response and is therefore meant to improve the biocompatibility of metallic implants (10). Studies regarding the safety of hydroxyapatite implants have shown no evidence of toxicity. Long-term clinical data have shown the biocompatibility and safety of hydroxyapatite coatings in clinical settings (10–14). Furthermore, Pezzantini et al. (14) have shown that in the presence of hydroxyapatite nanocrystals, endothelial cells maintain morphological and biochemical markers of a healthy functioning endothelium, without the acquisition of proinflammatory phenotypes (14).

The hydroxyapatite coating thickness is on the order of 500 to 700 nm and possesses porosity in the range of 100 to 500 nm in diameter. The oil-based carrier of sirolimus uniformly fills the porosity of the hydroxyapatite coating without adding to the thickness of the coating; therefore, the final drug delivery coating remains under 1 μm in thickness. Figure 1 shows the scanning electron micrograph pictures of the hydroxyapatite coating as well as the final coating system. Because of the minimal coating thickness, the amount of the carrier material for the drug is significantly minimized.

Current results have shown that the hydroxyapatite is stable for more than 4 months in an in vitro testing environment. The in vivo expected lifetime of the hydroxyapatite coating is in between 9 months and 1 year. After that period, it is expected to crack and disappear (100% according to pre-clinical data).

Antiproliferative agent sirolimus. Sirolimus (Rapamune), a natural macrocyclic lactone, is a potent immunosuppressive agent that was developed by Wyeth-Ayerst Laboratories (Madison, New Jersey) and approved by the Food and Drug Administration (FDA) for the prophylaxis of renal transplant rejection in 1999 (15). Sirolimus binds to an intracellular receptor protein and elevates p27 levels, which leads to the inhibition of cyclin/cyclin-dependent kinase complexes

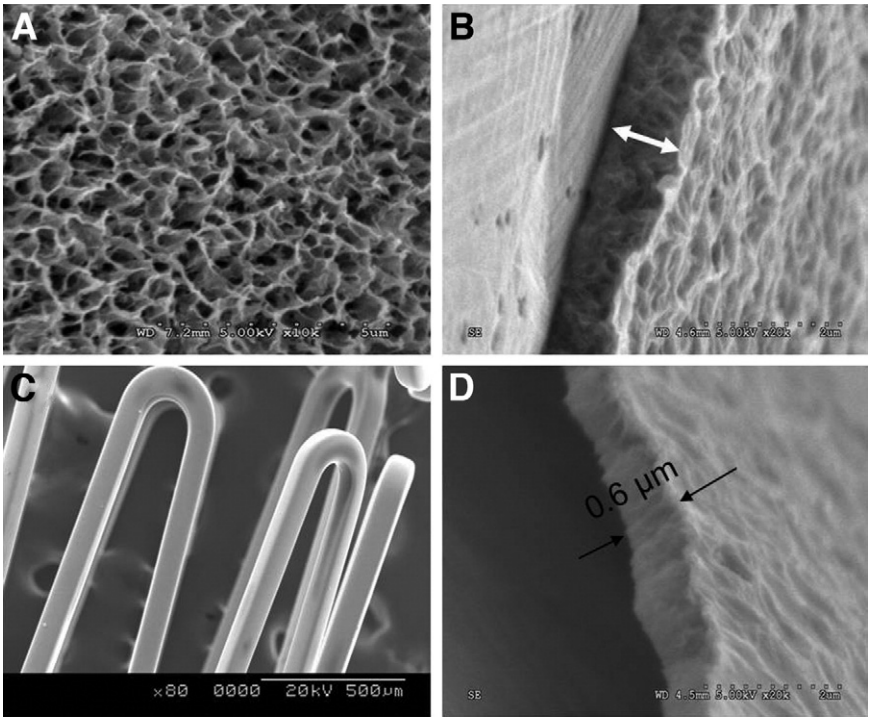

Figure 1. Main Components of the Vestasync Sirolimus-Eluting Stent System

Scanning electron micrographs of **(A)** microporous hydroxyapatite coating, **(B)** cross section of the hydroxyapatite coating, **(C)** final coating, including the hydroxyapatite filled with sirolimus formulation, and **(D)** cross section of the final coating.

and, ultimately, induces cell-cycle arrest in the late G1 phase. It inhibits the proliferation of both rat and human smooth muscle cells in vitro (16,17) and reduces intimal thickening in models of vascular injury (18–20).

Regarding sirolimus kinetics in the VES, in vitro testing on crimped and expanded stents at 37°C in 7.4 pH buffered saline demonstrates a drug release rate (in micrograms per time point, not percentage of loaded drug) that is almost the same as that of the Cypher stent for the first hour. Thereafter, the release rate slows down to less than half the rate of Cypher. By in vitro experimentation, it is calculated that 100% of the drug will be released from the stent in approximately 3 to 4 weeks.

Procedure. For the present study, the VES was available in only 2 diameters (3.0 and 3.5 mm) and a single length (19 mm). The eluted dose of sirolimus was less than half of the dose used in the Cypher stent (55 μg vs. 140 μg).

All interventions were performed according to the current standard guidelines. After mandatory predilation of the target lesion, stents were deployed with high pressure after dilation.

Dual antiplatelet therapy including loading dose of aspirin (200 to 325 mg) and thienopyridine (clopidogrel 300 mg) was started at least 24 h before the procedure. Postprocedural aspirin was continued indefinitely, and clopidogrel was maintained for 6 months (75 mg/day). During the procedure, intravenous heparin (70 to 100 IU/kg) was administered after sheath insertion to maintain an activated clotting time >250 s. Use of additional medications during the procedure, including glycoprotein IIb/IIIa inhibitors, was left to the operator's discretion.

A 12-lead electrocardiogram was obtained: 1) before the procedure; 2) immediately afterward; and 3) 24 h later. Blood sample laboratory analysis included cardiac enzymes creatine kinase (CK) and creatine kinase-myocardial band (CK-MB) before the procedure (<24 h) and 12 to 18 h after treatment.

Follow-up. After discharge, patients were clinically followed up by medical appointments at 1, 3, and 6 months. Additional clinical follow-up at 9, 12, and 24 months is expected by protocol. Angiography and intravascular ultrasound (IVUS) follow-up was scheduled for 4 months after the baseline procedure.

Quantitative coronary angiography (QCA) analysis. Angiographic studies were performed at baseline, after the procedure, and at follow-up, in 2 orthogonal views, after the intracoronary administration of 100 to 200 μg nitroglycerin. The same angiographic angles performed at baseline were reproduced at the subsequent studies. Digital angiograms

were analyzed off line with the use of an automated edge-detection system (QCA-CMS, Medis Medical Imaging Systems, Nuenen, the Netherlands). Lesion morphology was assessed by using standard criteria, and lesion complexity was defined according to the modified American College of Cardiology/American Heart Association (ACC/AHA) classification system (21). The contrast-filled catheter tip was used for calibration.

Quantitative angiographic parameters included: 1) reference vessel diameter; 2) minimum lumen diameter; 3) lesion length; 4) percent diameter stenosis (difference between the reference diameter and minimum lumen diameter divided by the reference diameter and multiplied by 100); and 5) late luminal loss (difference between minimum lumen diameter at the end of the procedure and minimum lumen diameter at follow-up). Quantitative analysis was performed in the in-stent area (inside the stented segment) and in the in-lesion segment, including the stented area as well as 5 mm both proximally and distally to the stent. In-stent and in-lesion restenoses were defined as ≥50% diameter stenosis at follow-up located within the stent and the target lesion, respectively.

IVUS analysis. The IVUS studies were performed immediately after the procedure and at follow-up, after intracoronary administration of 100 to 200 μg nitroglycerin.

All IVUS studies were performed with a motorized automatic transducer pullback system (0.5 mm/s) and commercially available scanners (i-Lab, Boston Scientific Corporation, Natick, Massachusetts) consisting of a rotating 40-MHz transducer catheter (Atlantis SR pro) with a 2.6-F imaging sheath. The images were digitalized for off-line quantitative analysis according to the American College of Cardiology's Clinical Expert Consensus Document on IVUS. Quantitative IVUS analysis was made using a commercially available computerized planimetry program (EchoPlaque, INDEC Systems, Mountain View, California).

Quantitative parameters of lumen, stent, and vessel (external elastic membrane) cross-sectional areas were determined. The neointimal area was calculated as the stent area minus the lumen area at follow-up. Late lumen area loss was calculated as the minimum lumen area after initial stent deployment minus the minimum lumen area within the stented segment at follow-up. Lumen, stent, vessel, and neointimal volumes were calculated using Simpson's rule. Percent of neointimal volume obstruction was determined by the neointimal volume at follow-up divided by the follow-up stent volume and multiplied by 100.

Incomplete stent apposition was defined as ≥1 stent strut clearly separated from the vessel wall with evidence of blood speckles behind the struts, and was classified as follows: 1) persistent (when present both in the post-stent implantation and follow-up studies); 2) late acquired (when not present at post-stent implantation, but detectable at the follow-up study); and 3) resolved (when present at post-stent implantation, but not detectable at the follow-up study).

Both QCA and IVUS analyses were performed by independent core laboratories at Cardiovascular Research Center (São Paulo, Brazil).

Study end points. The primary end points of this analysis were in-stent luminal late loss as measured by QCA and in-stent percentage volume obstruction by IVUS, measured at 4-month angiographic follow-up. Secondary end points included acute success (angiographic and procedure success), cumulative rate of major adverse cardiac events up to 2 years, rates of target lesion and target vessel revascularization up to 2 years, and in-stent volumetric neointimal burden by IVUS at 4 and 8 months.

Device success was defined by the presence of residual stenosis <20% in the treated segment, in the presence of Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 after implantation of the VES. Procedure success was defined by device success associated with no in-hospital major adverse events. A major adverse cardiac event was defined as death, nonfatal myocardial infarction (Q-wave and non–Q-wave), and need for repeat lesion revascularization (by new percutaneous intervention or coronary artery bypass graft surgery). All deaths were considered cardiac unless a clear noncardiac reason was identified. Myocardial infarction was defined by an increase in the CK-MB twice the upper the normal limit with or without new Q waves on the electrocardiogram.

Statistical analysis. Continuous variables are expressed as mean ± SD. Comparisons between post-intervention and follow-up measurements were performed with a 2-tailed paired *t* test. A p value < 0.05 was considered statistically significant.

Results

During May 2007, a total of 15 consecutive patients who matched the inclusion/exclusion criteria were treated with the Vestasync eluting stent and included in this analysis. The mean age was 63.8 years (± 1.4 years), and 40% were women. Diabetes mellitus was present in 33% of the cases. The left anterior descending artery was the target vessel in most cases (47%) (Table 1).

All stents were successfully deployed, and all patients were discharged without complications 24 h after the percutaneous intervention. Enzymatic elevation (CK and CK-MB) was not observed among these patients.

Post-procedure and 4-month QCA and IVUS results are displayed in Tables 2 and 3. One IVUS study was deemed inappropriate for analysis (poor image quality), and therefore the patient was excluded from the IVUS baseline/follow-up comparison. Binary restenosis (in-stent stenosis ≥50%) was not observed in any these patients by QCA, and no patient had more than 10% neointimal proliferation at

Table 1. Baseline Patient, Lesion, and Procedure Characteristics

Characteristics	Patients (n = 15)
Mean age, yrs	63.8 ± 11.4
Female	6 (40%)
Hypertension	9 (60%)
Dyslipidemia	7 (47%)
Diabetes mellitus	5 (33%)
Smoking	7 (47%)
Family history of CAD	6 (40%)
Previous MI	7 (47%)
Previous CABG	2 (13%)
Treated coronary artery	
LAD	7 (47%)
LCx	4 (25%)
RCA	4 (25%)
Lesion complexity*	
Type A	1 (7%)
Type B1	3 (20%)
Type B2	11 (73%)
Pre-dilation	15 (100%)
Post-dilation	7 (47%)
Number of stents per lesion	1.0
Mean final deployment pressure, atm	12.4 ± 2.1
Pre-procedure QCA	
Mean reference vessel diameter, mm	2.67 ± 0.32
Mean lesion length, mm	9.98 ± 1.98
Minimum lumen diameter, mm	0.98 ± 0.29
Diameter of stenosis	63.5 ± 9.90
Angiographic success	15 (100%)
Procedure success	15 (100%)

Values are mean ± SD or n (%). *According to American College of Cardiology/American Heart Association classification

CABG = coronary artery bypass graft; CAD = coronary artery disease; DS = diameter of stenosis; LAD = left anterior descending artery; LCx = left circumflex coronary artery; MI = myocardial infarction; RCA = right coronary artery; QCA = quantitative coronary angiography.

IVUS. Two cases of acute incomplete stent apposition were observed in the baseline procedure and were significantly reduced at 4-month follow-up. Figure 2 exemplifies the best and worst results of the patients enrolled in this study.

Table 2. Baseline (Post-Procedure) and 4-Month Quantitative Coronary Analysis

	Post-Procedure (n = 15)	4-Month Follow-Up (n = 15)
In-lesion MLD, mm	2.21 ± 0.36	2.05 ± 0.38
In-stent MLD, mm	2.64 ± 0.31	2.34 ± 0.33
In-lesion diameter of stenosis, %	20.5 ± 9.0	23.6 ± 8.8
In-stent diameter of stenosis, %	8.4 ± 4.3	13.8 ± 7.0
Acute gain, mm	1.66 ± 0.34	N/A
In-lesion late loss, mm	N/A	0.16 ± 0.29
In-stent late loss, mm	N/A	0.30 ± 0.25

Values are mean ± SD. The p value was not significant for any comparison between baseline and 4-month results.

MLD = minimum lumen diameter; N/A = not applicable.

Table 3. Intravascular Ultrasound Measurements at Baseline and 4-Month Follow-Up

Measurement	Baseline (n = 14)	4-Month Follow-Up (n = 14)
Vessel volume, mm^3	294.2 ± 117.1	286.9 ± 87.4
Stent volume, mm^3	144.5 ± 48.2	140.5 ± 36.7
Lumen volume, mm^3	144.7 ± 48.4	136.3 ± 34.2
In-stent neointimal volume, mm^3	N/A	4.3 ± 3.5
In-stent volume of obstruction, %	N/A	2.8 ± 2.2

Values are mean ± SD. The p value was not significant for any comparison between baseline and 4-month results.

N/A = not applicable.

At 6-month clinical follow-up, all patients were asymptomatic with negative results of noninvasive ischemia testing. There were no major adverse clinical events, including cardiac/noncardiac death, cerebrovascular accident, nonfatal myocardial infarction, or stent thrombosis.

Discussion

The main finding of this first-in-human study with the non–polymer-based VES is that sirolimus can be efficiently delivered to the coronary artery without a durable polymer, as demonstrated by the minimum neointimal growth noted at QCA and IVUS.

The development of novel DES systems must be guided by 2 main rationales: 1) to achieve an improved safety profile, and 2) to improve or at least keep the efficacy profile at levels comparable to those of the existing DES devices.

The DES toxicity may be related mainly to 2 aspects: dose/type of the antiproliferative agent delivered to the coronary artery and presence/type of polymer used to carry the antiproliferative drug. In this context, the novel VES carries less than one-half of the dose of the first-generation Cypher sirolimus-eluting stent. As previously demonstrated by Nakamura et al. (22), it is possible to keep the same efficacy of the Cypher stent using 70% or even 45% of its original dose. In a study conducted by that group with 44 patients treated with the Cypher stent at reduced doses, angiographic and ultrasonographic results were comparable to those obtained after the full-dose Cypher implantation (22). Our current analysis supports their findings.

A few recent clinical reports have correlated the presence of durable polymers to local vessel response (e.g., marked positive remodeling in the treated segment), and of more importance, some potentially life-threatening cases of late and very late stent thrombosis have been described. These clinical findings have also been associated with local inflammatory response, as noted in post-mortem studies (23,24).

At present, 4 different DES are FDA approved (Cypher, Taxus, Endeavor, and Promus/Xience V). Apart from the Endeavor, which uses a biocompatible polymer (phosphorycholine) to carry the zotarolimus, the other 3 systems use

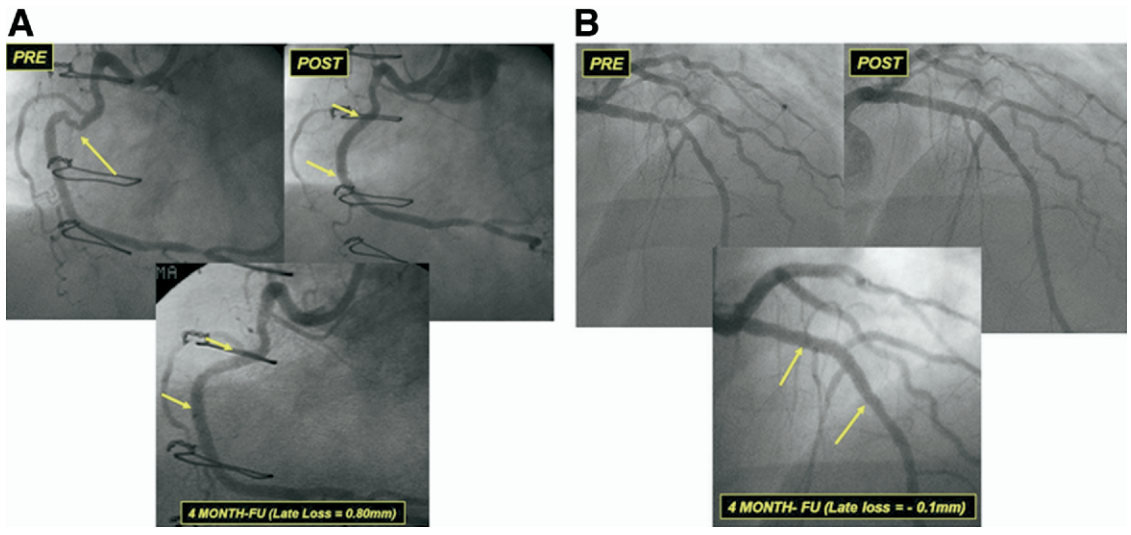

Figure 2. Examples From Our Initial Experience

Two examples of our first-in-human series of patients treated with the Vestasync stent. **Panel A** demonstrates the case with higher late lumen loss at 4 months (0.80 mm). **Panel B** demonstrates our best results (late lumen loss of −0.1 mm). FU = follow-up; POST = post-procedure; PRE = pre-procedure.

durable polymers. The Endeavor, though, is the DES that elicits more neointimal proliferation, as consistently demonstrated in all clinical studies (roughly 0.6 mm) (25). The other 3 DES presented late loss ranging from 0.1 to 0.4 mm in their clinical series (Fig. 3) (26–28). As demonstrated by Mauri et al. (29), there are incremental steps in binary restenosis as in-stent late loss increases. According to the mathematical model proposed by their group, a rise from 0.2 to 0.4 mm would result in an increase in restenosis rate by 3.1%, whereas an increase in late loss from 0.4 to 0.6 mm would result in an augmentation in the expected restenosis rate by 6.4%.

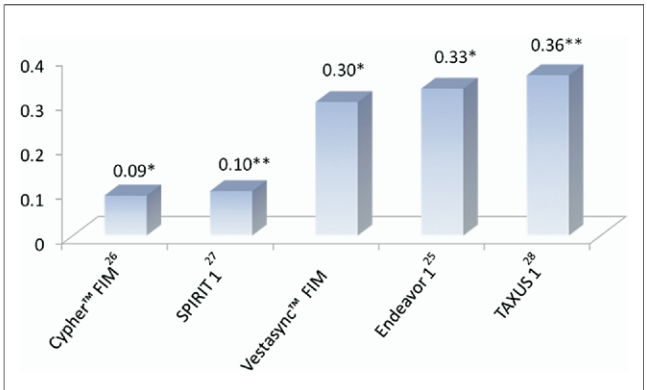

Figure 3. Late Lumen Loss of Vestasync Stent Versus the FDA-Approved DES

Late loss results reported for the Food and Drug Administration (FDA)–approved drug-eluting stent (DES) in contrast to the findings of the current analysis. When compared to the published results of other DES tested in similar scenarios, the in-stent late loss of the Vestasync stent is equivalent to that of the Endeavor and Taxus stents and slightly higher than that of the Cypher and Xience/Promus stents. *Invasive follow-up done at 4 months. **Invasive follow-up done at 6 months. FIM = first-in-man; SPIRIT = Stroke Prevention in Reversible Ischemia Trial.

The VES late loss of 0.30 mm situates this new device among the highest-efficacy DES, with the advantage of a polymer-free system using less drug than first-generation equivalents. Figure 2 exemplifies 2 cases of our preliminary series.

Currently ongoing, the multicenter Vestasync 2 trial will compare, in a randomized fashion, patients treated with the VES (n = 90) to its noneluted equivalent, the GenX stent (n = 30).

Study limitations. This study comprises a registry of only 15 patients with noncomplex coronary lesions with 6-month clinical follow-up. Considering the virtual absence of late loss (by QCA) and neointimal formation (by IVUS) at 4-month invasive follow-up, however, these results seem to be very promising. Nine-month angiography and IVUS will be performed in all patients to assess whether these preliminary findings are sustained; moreover, patients will be clinically followed up for 3 years. The 4-month follow-up of 15 patients precludes any definite conclusion about the long-term safety of this device.

Conclusions

The third-generation Vestasync hydroxyapatite non-polymer-based sirolimus-eluting stent system was proved feasible and safe, and elicited minimum neointimal proliferation at 4-month follow-up. These favorable preliminary

results require further confirmation by large, randomized, multicenter clinical studies with longer follow-up.

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